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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,793	01/11/2002	Victor Klimyuk	ICON-002	4086

530 7590 12/03/2004

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EXAMINER	
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ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,793	KLIMYUK ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1112002 & 7072003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-16, 18, and 20-28 in the reply filed on September 8, 2004 is acknowledged. It is noted, however, that unity of invention was found to exist during examination of international application PCT/US00/21461. Therefore the instant restriction requirement is withdrawn and all groups are rejoined. Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Claims 1-42 are examined in this Office action.

Information Disclosure Statement

2. The information disclosure statement filed July 3, 2003 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of the reference listed, which is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

3. Claim 16 is objected to because of the following informalities: the term, --acid-- should be inserted in line 2 after, "nucleic". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-16, 19-29, and 36-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 19, and 36: the claims are indefinite because their preambles are inconsistent with the last recited method steps. The preambles indicate that the methods are for making a plant artificial chromosome. However, the last step of the claims yields fused protoplasts or cells derived from them, or hybrid plant species or cells or protoplasts thereof. It is suggested that line 1 of claims 1 and 36 be amended by inserting, --plant protoplasts or cells comprising-- after "making", and that line 1 of claim 19 be amended by inserting, --a hybrid plant species comprising-- after "making".

In claim 2: the recitation, "irradiating" renders the claim indefinite. It is unclear what the protoplasts are to be irradiated with.

In claim 10: the claim indicates that plants are to be regenerated from the protoplasts of claim 1, step (a), before step (b). However, step (b) requires making chromosome fragments within the protoplasts of step (a). Claim 11 is indefinite because it does not yield the protoplasts that are to be used in step (b).

In claim 12: the recitation, "recombination site" renders the claim indefinite. It is not exactly clear what is meant by this recitation. For example, what is the difference between a recombination site and a restriction site?

In claim 20: the claim is indefinite because it is unclear whether the at least one plant chromosome fragment comprises the exogenous nucleic acid. It is suggested that the claim be amended by inserting at the end, --wherein the chromosome fragments contain the exogenous nucleic acid--.

In claims 29: the claim is indefinite for the same reasons as claim 20. It is suggested that the claim be amended similarly to claim 20.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20-35 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn towards isolated plant cells or protoplasts containing at least one plant chromosome fragment exhibiting normal plant chromosomal activities, produced by a method comprising production of chromosome fragments in protoplasts, followed by fusion with other plant protoplasts; or whole plant produced by regeneration of said protoplasts or cells;

seed derived from said plant; hybrid plant species or cells or protoplasts containing at least one chromosome fragment exhibiting normal plant chromosomal activities, produced by a method comprising crossing of an plant in which chromosome fragments were produced; or a recombinant nucleic acid comprising a first centromeric sequence functional in a plant cell and a second centromeric sequence functional in a yeast cell, wherein nucleic acid exhibits normal plant chromosomal activities; or a vector or recombinant cell of any species comprising said nucleic acid.

The specification indicates that protoplasts of a nitrate-reductase mutant of Nicotiana plumbaginifolia and Atropa belladonna were prepared. A. belladonna protoplasts were irradiated with gamma rays using a Co60 source and fused with N. plumbaginifolia protoplasts. The radiation inactivates the donor protoplasts. Calli following protoplast fusion were transferred to a solid medium and regenerated. A. belladonna chromosomes are significantly smaller than N. plumbaginifolia chromosomes. Minichromosomes were detected in the plants regenerated from the fused protoplasts that were significantly smaller than the A. belladonna chromosomes (Example 1). Mesophyll protoplasts were isolated from wild-type N. plumbaginifolia and transgenic, kanamycin-resistant Petunia hybrida plants. The Petunia protoplasts were irradiated with gamma rays, fused with the N. plumbaginifolia protoplasts, grown in kanamycin-supplemented medium, and plants regenerated. Metaphase plates and spreads were prepared for chromosome analysis. In most recovered lines, only Nicotiana chromosomes were detected. However, 2-3 chromosome fragments could be seen in one diploid and four tetraploid lines (Example 2). A vector, pYAC-GN, was also constructed that contained a p35S-APH(3')III-NOS3' gene, a p35S-GUS-NOS3' gene, a polylinker, and YAC sequences that can be used to

rescue plant minichromosomes in yeast cells. For two other vectors, a p35S:GUS:OCS3' cassette was inserted into pYAC4, which was then inserted into pBIN19, producing pIC461 and pIC462, depending on orientation. Protoplasts of transgenic plants carrying pYAC-GN, pIC461, or pIC462 were prepared, gamma-irradiated, and fused with non-irradiated protoplasts of N. plumbaginifolia. Recovered plants carried the N. plumbaginifolia genome and minichromosomes with YAC sequences and the kanamycin resistant gene (Example 2).

However, the specification does not adequately describe the genus of recombinant nucleic acids, vectors or recombinant cells comprising them; isolated plant cells, protoplasts, whole plants or seeds derived from them, or hybrid plant cells or species encompassed by the claims. Not all of the claimed products will share the same structures, as the nucleic acids comprised in the claimed recombinant nucleic acids, and the exogenous nucleic acids of the chromosome fragments of the protoplasts or plants produced by the claimed methods will be different. The claimed products will then have different functions, which are not shared by the other members of the genus of the claims. While the specification describes a few recombinant nucleic acids, isolated protoplasts, cells produced from them, and regenerated plants, produced by a method comprising the fusion of a gamma-irradiated plant protoplast and a non-treated protoplast, as discussed above, these products are not representative of the entire genus of recombinant nucleic acids, protoplasts, cells, plants and seeds encompassed by the claims, as they would have different structures and functions. While a method to produce such nucleic acids, protoplasts, cells and plants is discussed, a method of production does not describe the products themselves. See *Fiers vs. Sugarno*, 25 USPQ 2d (CAFC 1993) at 1606, which states that "[a]n adequate written description of a DNA requires more than a mere statement that it is

part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Further, the specification does not describe a single hybrid plant, cells or protoplasts thereof produced by a method comprising producing chromosome fragments of chromosomes in a plant, and then using that plant in a sexual cross. Given the breadth of the claims and the lack of written description as discussed above, the specification fails to provide an adequate written description of the multitude of isolated plant cells, protoplasts, plants, and seeds encompassed by the claims.

6. Claims 1-16 and 18-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making plant protoplasts or cells or hybrid plant species comprising a plant artificial chromosome by irradiating protoplasts with gamma radiation, does not reasonably provide enablement for the claimed methods by producing chromosome fragments in any other manner, or by producing chromosome fragments in whole plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn towards a method of making a plant artificial chromosome, comprising preparing recombinant protoplasts of a first plant species containing an exogenous nucleic acid, fragmenting the chromosomes within the protoplasts, fusing the recombinant protoplasts with protoplasts of the same or a different plant species, and identifying fused protoplasts or cells derived from them that contain chromosome fragments containing the exogenous nucleic acid and that exhibit normal plant chromosomal activities; or said method

wherein the chromosomes are fragmented by irradiating the protoplasts with any source or by contacting the protoplasts with any chemical agent; or wherein a whole plant is regenerated from said protoplasts or cells; isolated plant cells or protoplasts or plants, or seeds thereof produced by said method; or a method of making a plant artificial chromosome comprising producing transformed plants of a first plant species containing an exogenous nucleic acid, fragmentizing chromosomes within said plant, crossing said plant with a plant of the same or different species to produce a hybrid plant species; or hybrid plant species or cells or protoplasts thereof produced by said method.

The specification indicates that protoplasts of a nitrate-reductase mutant of Nicotiana plumbaginifolia and Atropa belladonna were prepared. A. belladonna protoplasts were irradiated with gamma rays using a Co60 source and fused with N. plumbaginifolia protoplasts. The radiation inactivates the donor protoplasts. Calli following protoplast fusion were transferred to a solid medium and regenerated. A. belladonna chromosomes are significantly smaller than N. plumbaginifolia chromosomes. Minichromosomes were detected in the plants regenerated from the fused protoplasts that were significantly smaller than the A. belladonna chromosomes (Example 1). Mesophyll protoplasts were isolated from wild-type N. plumbaginifolia and transgenic, kanamycin-resistant Petunia hybrida plants. The Petunia protoplasts were irradiated with gamma rays, fused with the N. plumbaginifolia protoplasts, grown in kanamycin-supplemented medium, and plants regenerated. Metaphase plates and spreads were prepared for chromosome analysis. In most recovered lines, only Nicotiana chromosomes were detected. However, 2-3 chromosome fragments could be seen in one diploid and four tetraploid lines (Example 2). A vector, pYAC-GN, was also constructed that contained a p35S-APH(3')III-

NOS3' gene, a p35S-GUS-NOS3' gene, a polylinker, and YAC sequences that can be used to rescue plant minichromosomes in yeast cells. For two other vectors, a p35S:GUS:OCS3' cassette was inserted into pYAC4, which was then inserted into pBIN19, producing pIC461 and pIC462, depending on orientation. Protoplasts of transgenic plants carrying pYAC-GN, pIC461, or pIC462 were prepared, gamma-irradiated, and fused with non-irradiated protoplasts of N. plumbaginifolia. Recovered plants carried the N. plumbaginifolia genome and minichromosomes with YAC sequences and the kanamycin resistant gene (Example 2).

However, the specification does not enable the fragmentation of chromosomes in plant protoplasts by any method other than gamma radiation. The specification mentions that chemical agents can be used to cause the chromosome fragmentation (page 7). However, the specification does not teach how any chemical agents are to be used with plant protoplasts or plants. Such direction is lacking in the prior art. In the absence of further guidance, undue experimentation would be required by one skilled in the art to determine how any chemical agents can be used to fragmentize chromosomes within plant protoplasts or plants such that they may still be used in the claimed methods. See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. The specification also does not teach other irradiation methods, other than gamma-radiation, to cause fragmentation of chromosomes within plant protoplasts. No guidance is provided at all as to what other types of light or radiation can be used. In the absence of further guidance, undue experimentation would be required by one skilled in the art to determine what other sources can

be used to irradiate plant protoplasts or plants such that chromosomes become fragmented, and the host can still be used in the claimed methods.

The specification also does not enable a method of making plants comprising plant artificial chromosomes wherein chromosome fragments are produced within plants, as encompassed by claims 19 and 29. The treatment that produces chromosome fragments renders the host non-viable (page 7). It is unclear how such treated plants may still be used in a cross, as required by claim 19. The prior art is also lacking in examples of such a method. In the absence of further guidance, undue experimentation would be required to treat plants in such a manner that causes chromosome fragmentation, while retaining viability and the ability to sexually reproduce. See Genentech, Inc. v. Novo Nordisk, A/S, *supra*.

Further, the specification does not enable the genus of recombinant nucleic acids encompassed by claims 30-35 and 42. The functions of the nucleic acids are not solely due to the centromeric sequences. The effect of that the nucleic acids have on the cells comprising them depend on the other sequences. The specification does not teach how to use all such other sequences. Further regarding claim 33: the claim broadly encompasses cells of all species. As the claimed recombinant nucleic acids are not functional in non-plant and non-yeast cells, it is unclear and not taught in the specification how one skilled in the art would use all host cells types encompassed by the claims. Given the breadth of the claims encompassing producing chromosome fragments within plant protoplasts in any manner or within whole plants, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 5-16, and 18-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Famelaer et al. (Theor. Appl. Genet., 1990, Vol. 79, pages 513-520) in combination with Blume et al. (Plant Journal, 1997, Vol. 12, pages 731-746) and Adam et al. (Plant J., 1997, Vol. 11, pages 1349-1358).

The claims are broadly drawn towards a method of making a plant artificial chromosome, comprising preparing recombinant protoplasts of a first plant species containing an exogenous nucleic acid, fragmenting the chromosomes within the protoplasts, fusing the recombinant protoplasts with protoplasts of the same or a different plant species, and identifying fused protoplasts or cells derived from them that contain chromosome fragments containing the exogenous nucleic acid and that exhibit normal plant chromosomal activities; or said method wherein the chromosomes are fragmented by irradiating the protoplasts with any source or by contacting the protoplasts with any chemical agent; or wherein a whole plant is regenerated from said protoplasts or cells; isolated plant cells or protoplasts or plants, or seeds thereof produced by said method; or a method of making a plant artificial chromosome comprising producing transformed plants of a first plant species containing an exogenous nucleic acid, fragmentizing

chromosomes within said plant, crossing said plant with a plant of the same or different species to produce a hybrid plant species; or hybrid plant species or cells or protoplasts thereof produced by said method.

Famelaer et al. teach the production of plants produced by fusing gamma-irradiated N. sylvestris protoplasts with non-treated N. plumbaginifolia protoplasts, and regeneration of plants therefrom. Chromosome fragments were detected in the plants, and progeny plants. Famelaer et al. assert that the technique can be applied to breeding programs, as it results in quicker introgression of desired traits (pages 513-518).

Blume et al. teach transgenic N. plumbaginifolia plants expressing the GUS selectable marker operably linked to an ACC oxidase promoter. The GUS coding region was inserted into restriction enzyme sites in a plant transformation vector prior to introduction of the vector into the plant (pages 732-738).

Adam et al. teach YAC vectors that can be used to stably transform plant cells (pages 1350-1353).

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to modify the method of producing hybrid plants of Famelaer et al. by producing protoplasts from the transgenic plants taught by Blume et al. and using them as the targets for irradiation. It was obvious that these or any protoplasts produced from other transgenic plants comprising any exogenous nucleic acid of interest could have been used as the protoplast to be irradiated. It was obvious that the chromosome fragments in the progeny plants of Famelaer exhibit normal plant chromosomal activities, as they were inherited from the plant regenerated from the fused protoplasts. It was also obvious that seeds were produced and

collected from the hybrid plant regenerated from the fused protoplasts, as progeny plants were produced. It also would have been obvious to produce cell cultures from the regenerated plant, for the purpose of propagation, for example. Any method of choice, including one comprising pulsed field gel electrophoresis, could have been used to select for fused protoplasts comprising chromosome fragments. It was also obvious that the protoplasts to be fused could be from the same or different plant species, as Famelaer et al. demonstrate that hybrid plants can be produced from fused protoplasts of different species. One would have been motivated to use such protoplasts comprising a transgene of interest, for the purpose of introgression of a desired trait into a desired recipient line. It also would have been obvious to further modify the method of producing hybrid plants by used the YAC vectors taught by Adam et al. comprising a transgene of interest to transform a plant prior to protoplast isolation, irradiation, and fusion with non-treated protoplasts. One would have been motivated to use such vectors, as they allow for introduction of genes from YAC libraries, and aid in subsequent isolation from plants. It would have been obvious that chromosome fragments inherited by progeny plants selected for the exogenous nucleic acid present on the YAC vector, would comprise centromeric sequences from the YAC vector that is functional in yeast cells, as well as centromeric sequences that allow for replication and inheritance in plant cells.

8. Claims 1-16 and 18-42 are rejected.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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November 28, 2004

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